

Chorionic Villus Sampling Compared With Amniocentesis and the Difference in the Rate of Pregnancy Loss

Aaron B. Caughey, MD, MPP, Linda M. Hopkins, MD, and Mary E. Norton, MD

OBJECTIVE: To compare loss rates following amniocentesis and chorionic villus sampling (CVS) over time.

METHODS: A retrospective cohort study of all amniocentesis and CVS procedures resulting in a normal karyotype from 1983–2003 at a single prenatal diagnostic referral center was conducted. Pregnancy loss rates for amniocentesis, CVS, and nonintervention groups (ie, those who had nuchal translucency screening or counseling, but no procedure) were compared using the χ^2 test. Year of procedure, maternal age, parity, race or ethnicity, and gestational age at procedure were controlled for in multivariable logistic regression models.

RESULTS: There were 9,886 CVS and 30,893 amniocentesis procedures performed during the study period that resulted in a normal karyotype. The overall loss rates were 3.12% for CVS and 0.83% for amniocentesis ($P < .001$). When examined by 5-year intervals, there was a statistically significant decrease in the CVS loss rate ($P < .001$) and a nonsignificant lesser decrease in the loss rate for amniocentesis over time. Although the pregnancy loss rate from CVS over the entire study period was higher than from amniocentesis (adjusted odds ratio 4.23, 95% confidence interval 2.29–7.81), in the most recent time period, 1998 to 2003, there was no difference between the two procedures (adjusted odds ratio 1.03, 95% confidence interval 0.23–4.52).

CONCLUSION: The loss rates for both amniocentesis and CVS at our institution have decreased over time. Because the decrease in loss rate for CVS has been greater, there is no longer a statistically significant difference between the two. These results are informative in both patient counseling and establishing widespread prenatal diagnostic and screening programs.

(*Obstet Gynecol* 2006;108:612–6)

LEVEL OF EVIDENCE: II-2

Prenatal diagnosis for fetal karyotyping or other genetic testing most commonly involves amniocentesis at 16–20 weeks of gestation, or chorionic villus sampling (CVS) at 10–12 weeks of gestation. Prenatal diagnosis of Down syndrome by amniocentesis was first reported in 1968,¹ and the CVS procedure was first described that same year.² Early amniocentesis, at 11–14 weeks gestation, has also been used, but is associated with higher loss rate and increased risk of fetal anomalies when compared with the other procedures.³

With recent data indicating the benefits of first trimester screening for chromosome abnormalities,^{4,5} it is likely that demand for early invasive diagnosis will increase. Further, a recent study demonstrated that of the 92% of women who would consider pregnancy termination, 50% would only do so in the first trimester.⁶ Thus, earlier prenatal diagnostic information is important for such women. Because the standard of care has been second trimester screening for aneuploidy, the introduction of first trimester screening for aneuploidy, assuming a 5% screen positive rate, may yield an additional 170,000 women aged younger than 35 years considering whether to undergo CVS to garner the earlier information such a procedure will provide.

Despite the need for data to counsel women considering invasive prenatal diagnosis, only four prospective, randomized controlled trials comparing

From the Division of Perinatal Medicine and Genetics, Department of Obstetrics, Gynecology & Reproductive Sciences, University of California, San Francisco, San Francisco, California; and Division of Health Services and Policy Analysis, School of Public Health, University of California, Berkeley, Berkeley, California.

Dr. Caughey is a Women's Reproductive Health Research Scholar, sponsored by the National Institute of Child Health and Human Development, Grant # HD01262.

Corresponding author: Aaron B. Caughey, MD, MPP, MPH, Assistant Professor, Department of Obstetrics and Gynecology, University of California, San Francisco, 513 Parnassus Avenue, Box 0132, San Francisco, CA; e-mail: abcnd@berkeley.edu.

© 2006 by The American College of Obstetricians and Gynecologists. Published by Lippincott Williams & Wilkins.

ISSN: 0029-7844/06



CVS to amniocentesis have been published to date,⁷⁻¹⁰ and the three largest of these studies were performed in the 1980s, soon after the introduction of this procedure. In the available data comparing CVS and amniocentesis, an early prospective trial found CVS to have a 0.4% greater rate of loss before 20 weeks of gestation and a 0.7% greater rate of loss up to 28 weeks of gestation.⁷ Another early nonrandomized study found a 0.8% increase in fetal loss after CVS as compared with midtrimester amniocentesis.¹¹ These findings have been validated as recently as 2002 in a retrospective study of 2,366 women in Australia.¹² It is unlikely such trials will be repeated in the future, because performing such trials has been demonstrated to be problematic with poor recruitment, particularly in the United States.⁴ However, loss rates from CVS seem to decrease with provider experience, and data currently used to counsel patients regarding the relative benefits of these two procedures was acquired when many providers were still gaining experience with the technique.

Given this background, we conducted the following study to answer several questions. What is the loss rate in patients undergoing CVS and amniocentesis when compared with patients who did not undergo procedures at our institution? Has the initial difference in pregnancy loss noted between CVS and midtrimester amniocentesis changed during the past 20 years?

METHODS

We designed a retrospective cohort study of all women who presented to the Prenatal Diagnosis Center at the University of California, San Francisco from 1983 to 2003 for any of the following indications: advanced maternal age, elevated risk on the expanded maternal serum alpha-fetoprotein (triple) screen, desired invasive prenatal diagnosis for other reasons, or desired nuchal translucency screening. All procedures were performed by either attendings or fellows who were either in or had completed a fellowship in maternal-fetal medicine or medical genetics. All providers performed a minimum of 50 amniocentesis or 100 CVS procedures under supervision. Exclusion criteria included multiple gestation, fetal aneuploidy, or detection of a major fetal anomaly. We obtained information on these patients that included obstetric history, gestational age at time of procedure, maternal age and ethnicity, type of procedure, year of procedure, and provider. The primary outcome examined was loss of pregnancy before 24 weeks of gestation. Outcome follow-up was obtained by sending a letter to the patient at the conclusion of

the pregnancy. If there was no reply, a genetic counselor called the referring physician. This led to the following follow-up rates: for women undergoing a CVS, the follow-up rate was 98.5%, for amniocentesis 98.1%, for nuchal translucency only 90.6%, and for second trimester counseling and ultrasound with no procedure 91.8%. Data obtained before 2000 were entered into a research database by trained data abstracters. After January 2000, data obtained at the time of the procedure as well as follow-up data were entered into a clinical database by the genetic counselors and physicians during the provision of clinical care. Because this same database is used to generate the clinical reports, the data are carefully reviewed several times for accuracy.

Because this was a retrospective study, we controlled for the difference in gestational age between CVS and amniocentesis in two ways. In univariable analyses, we compared the difference in pregnancy loss between those patients who had CVS and those who had only nuchal translucency to the difference between amniocentesis and those patients who presented in the second trimester for counseling and ultrasound for advanced maternal age or abnormal triple screen (increased risk for Down syndrome) but declined amniocentesis, because these pairs tended to have quite similar gestational ages. In multivariable analyses, we controlled for week of gestation as a continuous variable and conducted a cluster analysis by provider.

All data were entered into a STATA (StataCorp LP, College Station, TX) database. We compared the means of continuous variables with the Student *t* test. Univariable comparisons of proportions of pregnancy losses were made using the χ^2 test. The study cohort was divided into four time periods: 1983–1987, 1988–1992, 1993–1997, and 1998–2003. Assuming equal division of the procedures into the four periods and a baseline rate of loss among CVS of 1.5%, we estimated that the data would have greater than 80% power in each of the time subgroups to find a 50% difference between CVS and amniocentesis with a two-tailed alpha of .05. To assess changes in loss rates over time, the χ^2 test for trend was used. Multivariable logistic regression analysis controlling for potential confounders was used to generate odds ratios and 95% confidence intervals comparing CVS to amniocentesis. Differences were found to be significantly different with a *P* value of less than .05. Institutional review board approval for this study was obtained from the Committee on Human Research at University of California, San Francisco.



RESULTS

During the study period, there were 9,886 CVS and 30,893 amniocentesis procedures which met the study criteria and resulted in a normal karyotype. Women undergoing CVS were older and more likely to be white and multiparous (Table 1). They were also more likely to have the indication for the procedure be advanced maternal age. Overall, the pregnancy loss rate after CVS (3.12%) was greater than that of amniocentesis (0.83%, $P < .001$).

When the pregnancy loss rates were examined by 5-year intervals, the difference between CVS and amniocentesis was highest from 1983 through 1987 and lowest from 1998 through 2003 (Table 2). The loss rates for both CVS and amniocentesis seemed to decline over time. This decline was greater and statistically significant for CVS ($P < .001$) as compared with amniocentesis ($P = .270$). When the pregnancy loss rates were examined by maternal age, CVS loss rates were higher than amniocentesis loss rates in women both younger than and older than 35 years of age.

There were 1,292 women who underwent nuchal translucency ultrasound only, without an invasive procedure, for whom follow-up information was available. Of these, their mean age was 34.8 years, and 10 experienced spontaneous losses (0.77%). There were 2,138 women who had second trimester counseling and ultrasound due to advanced maternal age or elevated screening values but did not undergo an invasive procedure. They had a mean age of 33.4 years, and this group experienced 8 losses (0.37%). Using these loss rates to adjust the CVS and amnio-

Table 1. Population Characteristics

Variable	CVS (n=9,886)	Amniocentesis (n=30,893)	P
Mean maternal age (y)	37.1	35.6	<.001
Maternal age 35 y or older	86.5	75.2	<.001
Ethnicity			<.001
African American	1.5	3.5	
Asian	8.6	19.4	
Hispanic	4.6	11.4	
White	85.0	63.7	
Native American	0.2	2.0	
Mean gestational age (wk)	10.5	16.6	<.001
Nulliparous	34.5	38.6	<.001
Indication for procedure			<.001
Advanced maternal age	92.7	80.6	
Screening test positive	0.1	10.0	
Other: prior aneuploidy, prior NTD, anxiety	7.2	9.4	

CVS, chorionic villus sampling; NTD, neural tube defect.
Data are % unless otherwise specified.

Table 2. Crude Pregnancy Losses Postprocedure

Variable	CVS (n=9,886)	Amniocentesis (n=30,893)	P
All losses	3.12	0.83	<.001
Year of procedure			
1983–1987	4.36	0.91	<.001
1988–1992	2.93	0.89	<.001
1993–1997	3.05	0.72	<.001
1998–2003	1.93	0.64	<.001
P	<.001	.270	
Maternal age (y)			
Younger than 35	4.13	1.01	<.001
35 or older	3.05	0.79	<.001

CVS, chorionic villus sampling.
Data are % unless otherwise specified.

centesis loss rates, the differences were smaller, although still statistically significantly different (Table 3). After adjusting the amniocentesis loss rates for this background rate, the overall loss rate decreased to 0.46% and the rate from 1998–2003 decreased to 0.27% or 1 in 370.

When comparing by gestational age (Fig. 1), there is a clear decline in procedure-related loss rates from 9 through 15 weeks of gestation ($P < .001$ by χ^2 test for trend), whereas there seems to be no difference from 15 through 20 weeks of gestation ($P = .834$ by χ^2 test for trend).

When using multivariable logistic regression to compare the loss rates after CVS or amniocentesis across the entire 20-year period, there was a statistically significant difference (adjusted odds ratio 4.23, 95% confidence interval 2.29–7.81). However, the adjusted odds ratios decreased over time, becoming statistically nonsignificant from 1993 to 1997 and

Table 3. Adjusted* Pregnancy Losses Postprocedure

Variable	CVS (n=9,886)	Amniocentesis (n=30,893)	P
All losses	2.35	0.46	<.001
Year of procedure			
1983–1987	3.59	0.54	<.001
1988–1992	2.16	0.52	<.001
1993–1997	2.28	0.35	<.001
1998–2003	1.16	0.27	<.001
P†	<.001	.270	
Maternal age (y)			
Younger than 35	3.36	0.64	<.001
35 or older	2.28	0.42	<.001

CVS, chorionic villus sampling.
Data are % except where otherwise specified.

* Loss rates adjusted for first trimester nuchal translucency losses of 0.77% and second trimester counseling losses of 0.37%.

† P value is from a χ^2 test for trend between the different periods.



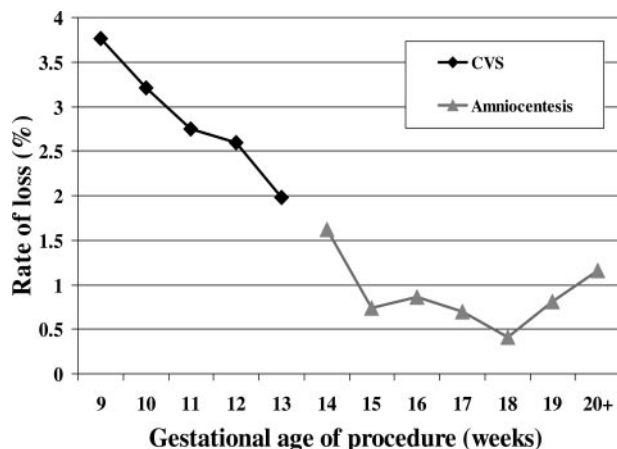


Fig. 1. Rate of loss by gestational age of procedure (CVS compared with amniocentesis). CVS, chorionic villus sampling.

Caughey. *CVS Compared With Amniocentesis*. *Obstet Gynecol* 2006.

becoming both statistically and clinically nonsignificant in the most recent period, 1998–2003 (adjusted odds ratio 1.03, 95% confidence interval 0.23–4.52) (Table 4).

DISCUSSION

In a cohort of women undergoing CVS or amniocentesis with normal karyotypes and nonanomalous fetuses, we found that the difference in pregnancy loss rates after these procedures decreased over time. In particular, we found no clinically or statistically significant difference between CVS and amniocentesis from 1998 to 2003. Such a finding, if replicated in other centers, is of paramount importance in this new era of first trimester aneuploidy screening.

With increasing availability of first trimester aneuploidy screening, access to CVS will need to ex-

pand to meet the needs of women who elect first trimester screening and diagnosis. If the risk of a pregnancy loss due to CVS is greater than amniocentesis, choosing between the two becomes a challenging decision, requiring women to balance the risks of the two with their preferences for the timing of information. The decision must also incorporate which actions will be taken in the face of such information, including the possibility of pregnancy termination. If there is no difference in risk between CVS and amniocentesis, the decision becomes much easier. Chorionic villus sampling would provide the information sooner and allow for an earlier, safer termination of pregnancy if so desired.

It is also important to note that the adjusted amniocentesis loss rate was 1 in 370 in the period from 1998 to 2003. This is much lower than the 1 in 200 loss rate commonly used to counsel women undergoing this procedure. The recent FASTER trial also reported an amniocentesis loss rate below the commonly quoted 1 in 200, although these results have not been published beyond abstract form (Simpson JL. Choosing the best prenatal screening protocol [editorial]. *N Engl J Med* 2005;353:2068–70). In the 1988 to 1992 period, the rate was 1 in 192. For CVS in the same two periods using the results from the multivariable analyses, the loss rate would be estimated at 1 in 34 women from 1988 to 1992 and 1 in 360 from 1998 to 2003. If indeed the loss rates after both amniocentesis and CVS have decreased, such information will be important to provide to patients considering these procedures.

Our study was not without limitations. Without question, the best study design to answer this question is a prospective, controlled trial of women randomized at 8–10 weeks of gestation before undergoing first trimester screening or counseling. In the nonrandomized setting, there are two major issues that may cause bias in the findings. The first is the different gestational ages at the time of the procedures (particularly between 9 and 15 weeks), because gestational age is strongly associated with pregnancy loss rates. We adjusted for this in two ways. The first was to estimate the background loss rate in women who presented in the first and second trimesters, but did not have a procedure. It is of note that women in both of the noninterventional groups, (ie, those undergoing nuchal translucency ultrasound and those presenting in the second trimester for counseling and ultrasound), were younger than those in the interventional groups. The mean maternal age for both noninterventional groups was just more than 2 years younger; thus the age-related effect on spontaneous abortion in

Table 4. Multivariable Analysis* of Pregnancy Losses Postprocedure Comparing CVS to Amniocentesis

Variable	Adjusted Odd Ratio	95% Confidence Interval	P
CVS compared with amniocentesis	4.23	2.29–7.81	<.001
Year of procedure			
1983–1987	19.56	7.65–50.03	<.001
1988–1992	5.69	1.47–22.02	.012
1993–1997	3.63	0.81–16.33	.092
1998–2003	1.03	0.23–4.52	.968

CVS, chorionic villus sampling.

*Models adjusted for maternal age, indication for procedure, provider, year of procedure, gestational age at procedure, race or ethnicity, and parity.



the two groups should be similar. The second way in which we adjusted for gestational age was to control for it in the multivariable analyses.

The other concern in a nonrandomized study is that of confounding. Although we controlled for potential confounders, there may exist other confounders of these procedures that we did not identify or have data available. For example, we did not have extensive data on socioeconomic status, including education or income level. Another limitation of this study is the concern that follow-up may differ among women who undergo a pregnancy loss as compared with those who do not. The overall follow-up rate was more than 97%, but if a larger percentage of women who undergo pregnancy loss are not reached, our findings may underestimate the true loss rates. Given that our overall procedure-related loss rates are consistent with those in the literature, we do not believe that this is a major consideration. Finally, even with a large number of procedures, power was an issue in the last time period. With the raw numbers and their difference, we had greater than 99% power to detect a difference between amniocentesis and CVS. However, we only had 71% power to detect a 50% difference in the adjusted rates.

Despite these limitations, we believe these findings are important for clinicians, patients, and policy makers alike. Clinicians can use this information, particularly with replication of these findings, to counsel their patients. Couples deciding whether to undergo CVS or amniocentesis can use the information to facilitate better decision-making. Finally, policy makers, particularly those at the level of training institutions should consider this information in light of first trimester screening to consider how to expand the number of providers trained in this procedure, so that women who wish to receive earlier diagnostic information will be able to do so.

REFERENCES

1. Valenti C, Schutta EJ, Kehaty T. Prenatal diagnosis of Down's syndrome. *Lancet* 1968;2:220.
2. Hahnemann N, Mohr J. Genetic diagnosis in the embryo by means of biopsy from extra-embryonic membrane. *Bull Eur Soc Hum Genet* 1968;2:23-9.
3. Randomised trial to assess safety and fetal outcome of early and midtrimester amniocentesis. The Canadian Early and Mid-trimester Amniocentesis Trial (CEMAT) Group. *Lancet*. 1998;351:242-7.
4. Wapner R, Thom E, Simpson JL, Pergament E, Silver R, Filkins K, et al. First-trimester screening for trisomies 21 and 18. *N Engl J Med* 2003;349:1405-13.
5. Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. *N Engl J Med* 2005;353:2001-11.
6. Learman LA, Drey EA, Gates EA, Kang MS, Washington AE, Kuppermann M. Abortion attitudes of pregnant women in prenatal care. *Am J Obstet Gynecol* 2005;192:1939-45.
7. Multicentre randomised clinical trial of chorion villus sampling and amniocentesis. First report. Canadian Collaborative CVS-Amniocentesis Clinical Trial Group. *Lancet* 1989;1:1-6.
8. Medical Research Council European trial of chorion villus sampling. MRC working party on the evaluation of chorion villus sampling. *Lancet* 1991;337:1491-9.
9. Smidt-Jensen S, Philip J. Comparison of transabdominal and transcervical CVS and amniocentesis: sampling success and risk. *Prenat Diagn* 1991;11:529-37.
10. Borrell A, Fortuny A, Lazaro L, Costa D, Seres A, Pappa S, et al. First-trimester transcervical chorionic villus sampling by biopsy forceps versus mid-trimester amniocentesis: a randomized controlled trial project. *Prenat Diagn* 1999;19:1138-42.
11. Rhoads GG, Jackson LG, Schlesselman SE, de la Cruz FF, Desnick RJ, Golbus MS, et al. The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. *N Engl J Med* 1989;320:609-17.
12. Scott F, Peters H, Boogert T, Robertson R, Anderson J, McLennan A, et al. The loss rates for invasive prenatal testing in a specialised obstetric ultrasound practice. *Aust N Z J Obstet Gynaecol* 2002;42:55-8.
13. Simpson JL. Choosing the best prenatal screening protocol [editorial]. *N Engl J Med* 2005;353:2068-70.

